Verbal and visual-spatial memory problems at adolescent age after neonatal extracorporeal membrane oxygenation

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Abstract

Objectives To assess neuropsychological outcome in 17- and 18-year–old neonatal extracorporeal membrane oxygenation survivors.

Design A prospective longitudinal follow-up study.

Setting Follow-up program at the Erasmus MC-Sophia Children's Hospital in Rotterdam, The Netherlands.

Patients Thirty adolescents 17 or 18 years old, treated between 1991 and 1997, underwent neuropsychological assessment.

Interventions None.

Measurements and Main Results Attention, memory, executive functioning, visual-spatial functions, social-emotional functioning, and behavior were assessed with validated instruments, and data were compared with reference data. Included predictors for analysis of adverse outcome were diagnosis, age at start extracorporeal membrane oxygenation, convulsions, and use of anti-epileptics. Adolescents' performance (expressed as mean [sd] z-score) was significantly lower than the norm on short-term and long-term verbal memory (z-score = -1.40 [1.58], p = 0.016; z-score = -1.54 [1.67], p = 0.010, respectively), visual-spatial memory (z-score = -1.65 [1.37], p = 0.008; z-score = -1.70 [1.23], p = 0.008, respectively), and working memory (32% vs 9% in the norm population). Parents reported more problems for their children regarding organization of materials (z-score = −0.60 [0.90]; p = 0.03) and behavior evaluation (z-score = −0.53 [0.88]; p = 0.05) on a questionnaire. Patients reported more withdrawn/depressed behavior (z-score = −0.47 [0.54]; p = 0.02), somatic complaints (z-score = −0.43 [0.48]; p = 0.03), and social problems (z-score = −0.41 [0.46]; p = 0.04). Patients reported more positive feelings of self-esteem and an average health status.

Conclusions Adolescents treated with neonatal extracorporeal membrane oxygenation are at risk of verbal, visual-spatial, and working-memory problems. Future research should focus on 1) the longitudinal outcome of specific neuropsychological skills in adolescence and adulthood; 2) identifying risk factors of neuropsychological dysfunction; 3) evaluating to what extent "severity of illness" is responsible for acquired brain injury; and 4) effects of timely cognitive rehabilitation.

Introduction

Neonatal extracorporeal membrane oxygenation (ECMO) stabilizes and supports critically ill newborns with acute and potentially reversible, respiratory failure(1). Worldwide, approximately 28,000 neonates have been treated with ECMO for this reason, with 75% surviving to discharge or transfer(2). The most common underlying conditions were meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), and persistent pulmonary hypertension of the newborn(2). The best results were obtained in MAS patients (94% survival) and the worst in CDH patients (51%)(2).

Survivors are at risk of serious complications, such as intra-cranial hemorrhage and infarctions(3). Internationally, routine neuroimaging during ECMO treatment showed abnormalities in 10–59% of infants, depending on case mix and case selection(3). In the Netherlands, the prevalence of brain injury during ECMO treatment was 17.3% nationwide(4). These findings alone are sufficient reasons for early identification of survivors at risk of adverse neurodevelopmental outcome and
close monitoring in the long-term. Moreover, critical illness, ECMO-treatment itself, and post-ECMO treatment factors may have consequences for outcomes in general.

Various studies have reported neuropsychological outcome of neonatal ECMO survivors until school age, showing that intellectual outcome did not differ from that of norm populations but that these children had deficits in attention, memory, and visual-spatial functions and more frequently had special educational needs(5–9). Neonatal ECMO survivors might be at risk of neuropsychological problems at older age because of the poor development of executive functioning, such as working-memory and planning. Executive functioning is needed to develop academic, behavioral, and social functioning and prepare for effective participation in society (e.g., finding a job). As these neuropsychological functions start to develop in early childhood but continue into young adulthood, these children may be at risk of "growing into deficits"(10). The aim of this study was to evaluate the neuropsychological outcome at adolescent age.

Materials and methods

Population

Data were obtained within the framework of a post-ECMO follow-up program—initiated in 2001 in our hospital—in which children's lung function, growth, and development are regularly assessed until 18 years old(11, 12). This study concerned 17- to 18-year–old adolescents who between February 1991 and June 1997 had been treated with neonatal venoarterial ECMO at the ICU of the Erasmus MC-Sophia Children's Hospital in Rotterdam. In all cases, the cannula had been placed by the same surgical team in the right cervical region. ECMO support was given in case of severe respiratory failure and an estimated mortality risk of higher than 80% using the entry criteria reported by Stolar et al(13). These criteria were: an oxygenation index (OI) greater than 40 beyond 4 hours or an alveolar arterial oxygen gradient greater than 600 during 6–8 hours, with an Fio2 of 100%, and signs of barotraumas or acute deterioration. During the study period, these entry criteria did not change in our institution.

The follow-up program is the standard of care for ECMO-treated neonates in the Netherlands(11, 12). The Erasmus MC Medical Ethical Review Board stated that "the Medical Research in Human Subjects Act (in Dutch: "WMO") does not apply to this study because subjects are not being submitted to any handling nor are there rules of human behavior being imposed". All participants and their parents provided permission to use the data.

Design

During the routine follow-up visit, structured questionnaires were used: parents of the adolescents provided information on socioeconomic status (SES; based on maternal education)(14) and ethnicity (at least one parent of Dutch/non-Dutch origin). Adolescents were asked about their academic achievement.

Overall intelligence was taken as the intelligence quotient (IQ) score at age 8 or 12 years. If IQ had been assessed at both ages, we used the IQ score assessed at 12 years. The follow-up program provides for a formal neuropsychological assessment by a pediatric psychologist. As part of the neuropsychological assessment, the parents filled out questionnaires in the waiting room of the hospital and the adolescents in the consultation room. In the first 10 years of the follow-up program, these assessments were limited and geared to individual needs, but from January 2012, a standard assessment battery was used for the neuropsychological tests (Supplemental Digital Content 1).

The following clinical data were retrieved: underlying disease (CDH, MAS, and other diagnoses); gestational age; birth weight; age at start ECMO; time on ECMO; highest OI and mean airway pressure prior to ECMO; duration of ventilation; oxygen dependency after extubation (< 1wk, 1wk to 1 mo, and > 1 mo); the presence of chronic lung disease (CLD) (15); abnormal cranial ultrasound (CUS: no and yes); use of morphine or other sedatives (< 1 wk, 1 wk to 1 mo, and > 1 mo); use of muscle relaxants (no, ICU: 1 d to 1wk, and ICU: > 1wk); the presence of convulsions (no, clinical but not tested, and confirmed on an electroencephalograph); use of antiepileptics (no, prophylactically, therapeutically < 1 mo, and therapeutically > 1 mo); and diagnosis of epilepsy at later age (no, yes, and dubious).

Instruments

Validated neuropsychological tests and questionnaires were administered in their Dutch versions to assess skills in different domains (see brief descriptions of the tests in the Supplemental Digital Content 1)(16–25).

Neuropsychological tests:

1. *Intelligence*: Wechsler Intelligence Scale for Children.
2. *Attention*: Trail Making Test and Stroop Color-Word test.
3. *Memory*: subtests Rebus Learning and Auditory Comprehension of the Kaufman Intelligence Test; subtest digit span of the Wechsler Adult Intelligence Scale; the Rey Auditory Verbal Learning Test (RAVLT); and the Rey Complex Figure Test (RCFT).
4. *Executive functioning*: Tower test.
5. *Visual-spatial processing*: RCFT copy.

Questionnaires:

1. *Executive functioning*: Behavior Rating Inventory of Executive Functioning (BRIEF; filled out by parents).
2. *Social-emotional functioning*: self-esteem: Self Perception Profile for Children (SPPC); health status: Pediatric Quality of Life Inventory (PedsQL).
3. *Behavior*: Youth Self-Report (YSR).

Data Analysis

Differences in medical and background characteristics (Table 2) between participants and nonparticipants were assessed with either the Mann-Whitney U test (continuous variables) or the chi square test (categorical variables). The assumption of normality were assessed.

To enable comparison of the results of the different neuropsychological assessments, all outcomes were converted into z scores (individual score minus the mean population score divided by the population sd). These z scores were compared with the z-score of IQ using paired sample t-tests. In this way, we analyzed whether the outcomes of the neuropsychological tests were concordant with IQ. Outcomes in z-scores on the neuropsychological tests and questionnaires were then compared with the z scores of the general population (mean z-score, 0; sd, 1) using paired samples t-tests. The difference between the digit-span forward and backward was assessed using the chi-square test.

The influence of each medical variable on the neuropsychological domains on which the adolescents showed impaired performance compared with the general population were assessed using univariate linear regression analyses. Those medical variables that were found to be significant predictors of impaired neuropsychological outcome were then added together – with SES as a covariate – in a multivariate linear regression model. To check the assumptions for linear regression analysis and to examine the applicability of the model, normal probability plots of the residuals and multicollinearity was evaluated (26).

All analyses were done using SPSS Statistics for Windows, Version 22.0 (IBM, Armonk, NY). A p value of 0.05 was used.

Results

Patients

Between February 1991 and June 1997, 72 neonates had been treated with ECMO. Eighteen (25%) had died prior to original hospital discharge (nine CDH; three MAS; six other diagnosis). Twenty of the 54 survivors (37%) did not attend follow-up at 17 years old: 11 refused, four had follow-up elsewhere, two only underwent medical examination because they had recently been tested elsewhere (MAS with developmental delay and other diagnosis with intellectual disability, respectively), two had emigrated, and one was not seen because of organizational reasons. For 17 of these 20 patients, data on outcome or state of health were available. Seven had average intelligence (one with epilepsy and an infarct, one with attention deficit hyperactivity disorder, and one with attention deficit disorder), six had developmental delay, and four had intellectual disability (one with epilepsy and one with attention deficit hyperactivity disorder). Most medical and background characteristics did not statistically differ between participants and nonparticipants; the exceptions are abnormal CUS, use of muscle relaxants, and the presence of convulsions (Table 1).

Neuropsychological assessment and questionnaires

Of the 34 adolescents (63%) attending follow-up, three had abnormal CUS as neonates (occlusion of the middle and anterior cerebral artery, subependymal hemorrhage grade 1, and watershed stroke, respectively).

Of all 34 participants, three could not complete the assessment battery because of intellectual disability and/or behavioral problems and only filled in questionnaires on self-esteem, health status, and behavior (CDH with intellectual disability, MAS with intellectual disability and possible autism, and CDH with intellectual disability [including a chromosome X duplication] and autism, respectively). For organizational reasons, one other patient (CDH with average intelligence) was not tested and only filled in the questionnaires. The other 30 adolescents had been assessed at the age of 17 or 18 years, but not all had performed all tests because of the fact that the follow-up assessments were first geared to individual needs and standardized from January 2012 (Table 2). The assumption of normality was met for the neuropsychological data and questionnaires.

Academic achievement

Of the 30 adolescents assessed at age 17 or 18 years, five were enrolled in special education (15%), eight in secondary education (24%; two in preparatory vocational secondary education and training [in Dutch: VMBO], five in Senior General Secondary Education [in Dutch: HAVO], and one in University Preparatory Education [in Dutch: VWO]). Twenty adolescents were enrolled in senior secondary vocational education and training (60%; in Dutch: MBO), and one (3%) was enrolled in first cycle higher education (in Dutch: HBO).

In the Dutch population, 6% of adolescents who are 17 and 18 years old attend special education, 27% secondary education, 49% vocational education, and 18% first cycle higher education(27). The percentages differed significantly from the reference norm (chi-square test, 63.8; $p < 0.001$).

Neuropsychological outcome

<u>Intelligence</u>

Based on outcomes of intelligence tests at 8 years (n = 3) or 12 years (n = 27), the mean IQ (sd)for the entire group was calculated to be 90.3 (19.4). The mean IQ z score was -0.65 (1.29), which is significantly below the norm of the Dutch population ($p = 0.03$). Six children

had scored below 70 at age 8 or 12 years. When those six were removed from the analyses, the IQ of the remainder of the group was 97.5 (13.8).

Attention

Selective and divided attention did not differ from what was expected based on their IQ (Table 2).

Memory

The adolescents scored significantly lower (Table 2) on short-term and long-term verbal (RAVLT immediate and delayed recall) and visual-spatial memory (RCFT immediate and delayed recall) than what was expected based on their IQ (Table 2). One adolescent had visual problems that could primarily affect the RCFT results but was able to copy the figure (RCFT copy) without major problems, indicating specific visual-spatial memory problems to explain the low scores on the RCFT immediate and delayed recall.

The adolescents scored significantly higher (Table 2) than expected based on their IQ on auditory short-term memory (digit span). However, the proportion of adolescents scoring lower on the backward span than on the forward span (indicative of a working-memory problem [28]) was significantly higher than the norm population (25) (32% vs 9%; $p < 0.01$).

Executive Functioning

The adolescents scored significantly higher (Table 2) than expected based on their IQ on the Tower test, which measures planning.

Visual-spatial processing

Results did not differ from what was expected based on their IQ (Table 2).

Questionnaires

Executive Functioning

Figure 1 graphically shows that the parents of the entire group on average evaluated executive functioning of their children to be less positive than that of the normal population (BRIEF organization of materials: mean [sd] = -0.60 [0.90], $p = 0.03$; BRIEF behavior evaluation: mean [sd] = -0.53 [0.88], $p = 0.05$).

Self-Esteem

The adolescents on average evaluated their behavior more positive than the reference population (SPPC behavior: mean [sd] = 0.67 [1.00], $p < 0.01$).

Health Status

The adolescents' health status on average did not significantly differ from that of the normal population. The adolescents rated their physical, emotional, social, school, and psychosocial functioning similarly to healthy peers (PedsQL physical functioning: mean [sd] = 0.25 [1.06]; PedsQL emotional functioning: mean [sd] = 0.49 [0.92]; PedsQL social functioning: mean [sd] = 0.06 [1.08]; PedsQL school functioning: mean [sd] = -0.01 (1.14); PedsQL psychosocial functioning: mean [sd] = 0.24 [0.95]).

Behavior Problems

The adolescents on average reported more internalizing behavior problems than found in the normal population (YSR withdrawn/depressed: mean [sd] = -0.47 [0.54], p = 0.02; YSR

somatic complaints: mean [sd] = -0.43 (0.48), $p = 0.03$; YSR social problems: mean [sd] = -0.41 [0.46], $p = 0.04$) (Fig. 1).

Factors influencing neuropsychological outcome

Regression analyses were performed to assess whether any medical characteristics (Table 1) could predict the four neuropsychological outcome variables that were significantly lower than in the normal population (RAVLT, both immediate and delayed recall; RCFT, both immediate and delayed recall).

First, univariate regression analyses with all medical variables identified four medical variables with an individual significant influence on one or more of the outcome variables: diagnosis, age at start ECMO, the presence of convulsions, and use of antiepileptics (Table 3). Next, multiple regression analyses were done with these four medical variables while correcting for SES. In the analyses, multicollinearity was evaluated. The multivariate regression model showed none of the medical variables to be significant predictors once added all together.

Discussion

In this first worldwide study of neuropsychological outcome of neonatal ECMO survivors at adolescent age, we found that short-term and long-term verbal deficits and visual-spatial memory problems were present in a large proportion of these adolescents, even after adjustment for IQ. Impaired visual acuity could have caused the poor visual-spatial memory results (RCFT immediate and delayed recall) in our study. One adolescent indeed had visual problems but still was able to copy the figure (RCFT copy) without major problems. Therefore, we believe that our results indicate specific visual-spatial memory problems in this population. Poorer processing skills combined with poor spatial abilities and lower scores on visual memory testing have been reported in 7-year-old neonatal ECMO survivors(8). Our findings suggest that these problems may persist into later life and could possibly affect academic performance and participation in society.

In this study, the subjects performed significantly better than expected based on their IQ on auditory short-term memory (digit span). The digit span is comprised of a forward span and a backward span component. The forward component requires more from short-term auditory memory(29), whereas the backward component requires more from working-memory (28) and may evoke more visuospatial image processes(30). Almost one-third of adolescents in this study scored significantly lower on the backward component than on the forward component compared to 9% in the norm population(25), suggesting deficits in working-memory. Deficits in working-memory have been identified in children with acquired brain injury as well(31).

Concerning the adolescents' executive functioning skills, in this study, parents reported more problems compared with the reference norm on the scales organization of materials and behavior evaluation in the adolescents. In practice, this could mean, for example, that they have difficulty in organizing homework assignments or do not evaluate their work after they have finished. We did not assess these specific executive functions, only planning. Further research should make clear whether the problems, reported by the parents, could be because of other poor executive functioning skills or (working)memory problems.

The key brain regions supporting working-memory are the dorsolateral and ventrolateral prefrontal and parietal cortex(32). These regions are also involved in organization skills and behavior evaluation (functions that parents reported to be suboptimal in their children). It would, therefore, be worthwhile to specifically study these brain regions in neonatal ECMO survivors with the use of neuroimaging. Another brain region, the hippocampus, is highly and selectively susceptible to injury caused by hypoxia-ischemia (including ECMO treatment) (33–36) and has been shown to lead to memory dysfunctions in later childhood (33). This type of injury might be a partial explanation for the verbal and visual-spatial memory problems found in this study. Neuroimaging studies should, therefore, also focus on the more subcortical located hippocampus.

Regarding social-emotional functioning, the adolescents reported more withdrawn behavior and somatic and social problems compared with the norm population. On the other hand, they had a significantly more positive feeling of self-competence. This is not an unusual finding. In a study with adolescent, preterm born children, the vast majority were content with their activities and participation in society although most of them were neither at school nor employed at age 19(37). In the same vein, we have previously found that self-reported emotional functioning of children with congenital anomalies treated with or without neonatal ECMO was not affected at the age of 8 years (7).

We were unable to identify significant predictors of the memory problems. Still, we believe that "severity of illness" is a predictor for neuropsychological outcome of neonatal ECMO survivors, rather than ECMO treatment itself. This notion is supported by findings for

children with CDH who were not treated with ECMO(7). Outcome after neonatal ECMO treatment is determined by many different factors: pretreatment related (e.g., congenital anomalies or loss of cerebral autoregulation), treatment related (such as intracranial hemorrhage), and posttreatment related (e.g., CLD and prolonged hospitalization)(9). However, a specific severity of illness scoring system for ECMO treated patients is not available(38). We believe that the lack of such a scoring system – together with the small sample size – may explain why we did not find significant predictors of outcome at older age.

This study has some limitations. First, only 63% of participants in the follow-up program had been assessed at adolescent age. We started our follow-up program in 2001, and therefore, a large proportion of the survivors was invited a long time after their treatment. This resulted in a small sample. In other studies with participants born from 1996 onward, we had participation rates above 85%(11, 12). Bias may have occurred because significantly more nonparticipants than participants had abnormal CUS during ECMO(Table 1). Second, the fact that the average IQ was significantly below the norm is a potential source of bias. In previous studies in (pre)school-aged ECMO survivors, intelligence was found to be equal to the norm(7, 8, 11). We assume that the generally low SES in this study contributes to the low IQ in this group, as low SES is associated with poorer cognitive development(39). To avoid confounding the neuropsychological outcome, we corrected for both IQ and SES in the statistical analyses. Further to this issue, the use of IQ obtained at 8 and 12 years old, rather than at adolescent age, could be considered a limitation. However, previous evidence that intelligence is stable from infancy into adolescence (40) was confirmed for the 14 adolescents who were evaluated at both 8 and 12 years this study. Third, we addressed selective and divided attention but not sustained attention. In a previous study, we found sustained attention problems in 8-year-old children treated with neonatal ECMO (7). Because poor sustained attention can interfere with memory, it is not clear whether the observed memory problems are primary or secondary dysfunctions. Fourth, we did not correct for multiple testing (n = 20) in the analyses of the neuropsychological tests. If we had done so, none of the results would have been significant. We decided to present the uncorrected results because this first study on neuropsychological outcome in neonatal ECMO survivors at adolescent age yields further directions for improvement of care and future follow-up studies. Fifth, we did not have a control group of adolescents who had similar severity of illness in the neonatal period but who did not undergo ECMO treatment. With two ECMO centers in the Netherlands, covering a relatively small geographical area, the large majority of neonates with similar severity of illness who are not born prematurely (i.e., born after 34 wk of gestation with birth weight > 2,000 gm) are treated with ECMO. Therefore, it will be difficult to obtain controls with similar severity of illness who survived without ECMO. As an alternative, patients from countries with less access to ECMO treatment could serve as controls. However, variety in treatment protocols and neuropsychological assessments may bias the results of such a study. For similar reasons, we consider the use of a historic control group of infants treated before the ECMO era not appropriate.

Despite the limitations, this study is of value as it is the first reporting on neuropsychological outcome following neonatal ECMO at 17–18 years and has important implications for patient care. Considering that we found neuropsychological deficits persisting into adolescence—thereby extending the evidence of “growing into deficit” in these patients—it is of utmost importance that we report outcome at this age in order to understand at which neuropsychological processes interventions should be aimed.

Conclusions

This study showed verbal, visual-spatial, and working-memory problems in adolescents of 17–18 years old treated with neonatal ECMO. Furthermore, parents reported some aspects of executive functioning as impaired in their children. Positively, health status and sense of self-competence did not seem affected. Considering the findings of this study in light of the outcome at school-age, future research should focus on 1) the longitudinal neuropsychological outcome, specifically of (working) memory, 2) developing a standardized scoring system to quantify "severity of illness", 3) evaluating to what extent "severity of illness" is responsible for acquired brain injury, and 4) evaluation of effects of cognitive rehabilitation (which is currently performed in our department). To achieve these goals, it would be necessary to set up multicenter follow-up programs with internationally standardized assessment instruments and neuroimaging.

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Tables

Table 1. Medical and background variables

	n=36 participants	n=18 non-participants	*p* value
Diagnosis, No. (%)			0.34
MAS	22 (61)	9 (50)	
CDH	5 (14)	1 (6)	
Other	9 (25)	8 (44)	
Gestational age in weeks, median (range)	40 (34-43)	40 (35-42)	0.94
Birth weight in grams, median (range)	3295 (2160-4980)	3220 (2300-4360)	0.99
Age start ECMO in hours, median (range)	28 (8-600)	25 (8-120)	0.26
Time on ECMO in hours, median (range)	122 (47-309)	127 (72-510)	0.65
Highest oxygenation index prior to ECMO, median (range)	54 (27-130)	55 (32-95)	0.81
Highest mean airway pressure prior to ECMO (cm H_2O), median (range)	21 (14-28)	20 (16-26)	0.63
Duration of ventilation in days, median (range)	10 (4-37)	10 (5-34)	0.95
Oxygen dependency post extubation, No. (%)			**0.04**
1 day- 1 week	18 (50)	7 (39)	
>1 week- 1 month	6 (17)	6 (33)	
>1 month	9 (25)	-	
Missing	3 (8)	5 (28)	
CLD, No. (%)			0.16
yes	10 (28)	1 (5)	
Missing	3 (8)	4 (22)	
Abnormal cranial ultrasound, No. (%)			**0.04**
yes	5 (14)	7 (39)	
Missing	-	1 (6)	
Use of morphine or other sedatives, No. (%)			0.77
<1 week	11 (31)	6 (33)	
1 week- 1 month	21 (58)	8 (44)	
>1 month	4 (11)	3 (17)	
Missing	-	1 (6)	
Use of muscle relaxants, No. (%)			0.09
No	3 (8)	-	
Intensive Care Unit 1 day- 1 week	20 (56)	14 (78)	
Intensive Care Unit >1 week	13 (36)	2 (11)	
Missing	-	2 (11)	
Presence of convulsions, No. (%)			**0.007**
No	25 (69)	10 (56)	
Clinical, but not tested	10 (28)	2 (11)	
Confirmed on electroencephalograph	1 (3)	6 (33)	
Use of anti- epileptics, No. (%)			0.26
No	14 (39)	4 (22)	
Prophylactically	11 (31)	6 (33)	
Therapeutically <1 month	5 (14)	1 (6)	
Therapeutically >1 month	6 (17)	7 (39)	
Diagnosis of epilepsy at later age, No. (%)			-
No	27 (75)	-	
Yes	3 (8)	-	
Dubious	3 (8)	-	
Missing	3 (8)	18 (100)	
Male gender, No. (%)	17 (47)	11 (61)	0.40

Medical and background variables (continued)			
Ethnicity, No. (%)			0.25
Dutch	24 (67)	8 (44)	
Missing	-	9 (50)	
SES, No. (%)			0.95
Low	19 (53)	5 (28)	
Moderate	12 (33)	4 (22)	
High	3 (8)	1 (6)	
Missing	2 (6)	8 (44)	

[a.] Results are presented as n (%) or median (range). MAS = meconium aspiration syndrome; CDH = congenital diaphragmatic hernia; other = persistent pulmonary hypertension in the newborn (n=7), sepsis (n=5), asphyxia (n=3), pulmonary hypoplasia due to kidney failure (n=1), respiratory syncytial virus (n=1); ECMO = extracorporeal membrane oxygenation; CLD = chronic lung disease as defined by Jobe and Bancalari(15). SES = socio-economic status based on maternal education(40).
P value: difference between participants and non-participants; the Mann-Whitney test was used for continuous variables; the chi-square test was used for categorical variables.

Table 2. Overview of neuropsychological assessment outcome

Neuropsychological test	n	IQ mean (SD)	Mean (SD)	*p* value
Attention				
TMT A	22	-0.69 (1.36)	-0.71 (1.75)	0.95
TMT B			-0.90 (1.28)	0.39
TMT B/A			-0.50 (0.93)	0.34
Stroop 1	22	-0.69 (1.36)	-0.94 (1.59)	0.18
Stroop 2			-0.79 (1.56)	0.74
Stroop 3			-0.90 (1.33)	0.45
Stroop			-0.41 (1.08)	0.34
Memory				
KAIT rebus learning	29	-0.59 (1.28)	-0.83 (1.11)	0.38
KAIT rebus learning delayed			-0.74 (1.56)	0.82
KAIT auditory comprehension			-0.34 (0.87)	0.22
KAIT auditory comprehension delayed			-0.70 (1.24)	0.63
WAIS Digit span	22	-0.69 (1.36)	-0.12 (1.12)	**0.014**
RAVLT immediate	28	-0.63 (1.33)	-1.40 (1.58)	**0.02**
RAVLT delayed			-1.54 (1.67)	**0.010**
RAVLT recognition	14	-0.66 (1.24)	-0.69 (1.53)	0.76
RCFT immediate	9	-0.47 (1.21)	-1.65 (1.37)	**0.008**
RCFT delayed			-1.70 (1.23)	**0.008**
RCFT recognition			-1.07 (0.69)	0.20
Executive functioning				
Tower	29	-0.64 (1.32)	-0.06 (0.96)	**0.03**
Visual spatial processing				
RCFT copy	9	-0.47 (1.21)	-0.97 (1.48)	0.29

[b.] n= number of adolescents assessed with that specific neuropsychological test. IQ mean (SD) = average z-score IQ of the adolescent group assessed with that specific test. Mean (SD) = average z-score of the neuropsychological test. *P* value = outcome of the paired samples t-test between IQ and neuropsychological outcome. ***P* value** = significant outcome of the paired sample t-test. TMT = Trail Making Test; Stroop = Stroop Color Word Test; KAIT = Kaufman Adult Intelligence Test; WAIS = Wechsler Adolescent Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test; Tower = Tower test.

Figures

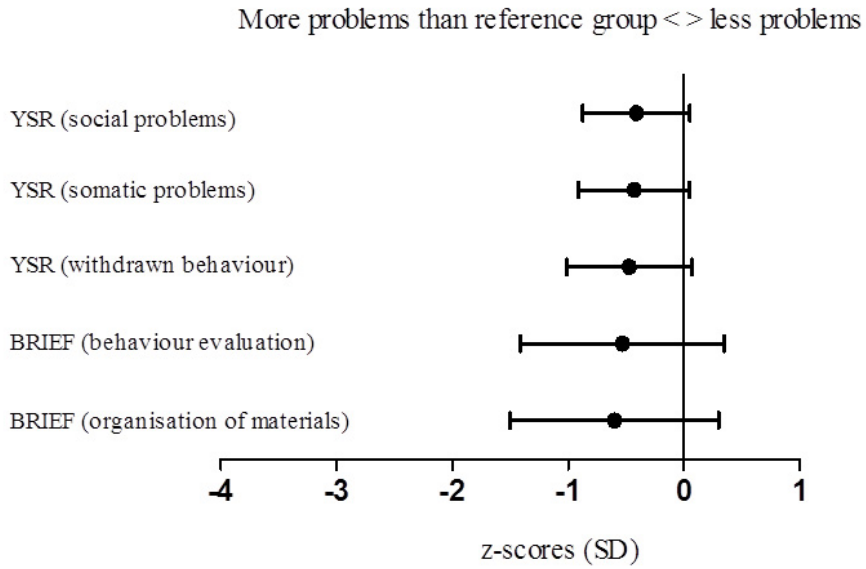

Figure 1.
YSR = Youth Self Report.
BRIEF = Behavior Rating Inventory of Executive Functioning.
Z-score = Individual norm score minus the population norm score divided by the standard deviation of the population.

Supplemental Material

Supplemental Digital Content 1. Descriptions of the neuropsychological tests.

Intelligence

Wechsler Intelligence Scale for Children (WISC-III-NL)

Intelligence test for children between the ages 6 and 16. The test generates a full scale IQ (FSIQ), Total Verbal IQ (TVIQ) and Total Performance IQ (TPIQ). The IQ scores are derived from five verbal and five performance subtests. There are also three supplemental tests (1, 2).

Attention

Trail Making Test (TMT)

This paper and pencil test consists of two parts. In the first part (part A), the subject must draw lines to consecutively connect numbered circles on a sheet. In the second part (part B), the subject must consecutively but alternately connect numbered and lettered circles on another worksheet. The goal of the test is to finish each part as quickly as possible. The test can be administered to children and adults in the age range 6-89 years. This test measures visual conceptual and visuomotor tracking as well as divided attention (3, 4).

Stroop Color Word Test (Stroop)

The Stroop consists of three trials: in the first trial (Stroop 1) the subject must read color names, in the second trial (Stroop 2) name printed colors, and in the third trial (Stroop 3) name printed colors not denoted by the color name. The test can be administered to children and adults in the age range 8-65 years. Selective attention is measured with this test (3, 4).

Memory

Kaufman Intelligence Test (KAIT) – subtest Rebus Learning

The subject learns a word or concept associated with a rebus (a picture that stands for a word) and then has to read aloud phrases and sentences that are composed of these rebuses. This is repeated after 30 minutes.

This test measures short- and long-term visual/verbal associative memory. Adolescents and adults in the age range 14-85 years can take the test (5, 6).

Kaufman Intelligence Test (KAIT) – subtest Auditory Comprehension

The subject has to listen to a recording of a news story, then answer literal and inferential questions about the story. This test measures short- and long-term (after 45 minutes) verbal memory and verbal logic reasoning. Adolescents and adults in the age range 14-85 years can take the test (5, 6).

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) – subtest Digit Span

The Digit Span consists of random number sequences that increase in length and that the examiner reads aloud at the rate of 1 number per second. The subject has to reproduce these numbers in the same order. Next, the sequences must be recalled backwards (3-5-7 becomes 7-5-3). The first part of the test measures short-term auditory memory and short-term retention capacity. The second part measures auditory working memory. A difference of 4 or more points between forward and backward Digit Span in favor of forward is indicative of a working-memory problem. The test is applicable to adolescents and adults in the age range 16-85 years (7).

Rey Auditory Verbal Learning Test (RAVLT)
The RAVLT consists of five presentations with recall of a 15-word list, a sixth recall trial after 30 minutes, and a seventh recognition trial. This test measures memory span, short- and long term verbal memory, verbal recognition, learning curve, and retroactive or proactive interference. It can be administered to children and adults in the age range 6-89 years (8, 9).

Memory and visual-spatial functioning
Rey Complex Figure Test (RCFT)
The RCFT consist of three trials. First the subject has to copy a complex figure. Then after 3 and after 30 minutes the figure must be drawn from memory. Next, different figures are shown and the subject has to indicate whether these figures were in the original figure. This test measures visual integration, short- and long-term visual-spatial memory, and visual-spatial recognition. It can be completed by children and adults in the age range 6-89 years (4, 10).

Executive functioning
Tower Test (Tower)
The subject must plan ahead to rearrange five colored rings in varying sizes from the initial position on three upright sticks to a new predetermined position in as few moves as possible. When two or more rings are at the same stick, the smaller ones must always be on top of the larger ones. Only one ring can be moved at the same time. This tests measures planning ability and can be administered to children and adults in the age range 8-89 years (11, 12).

Behavior Rating Inventory of Executive Functioning questionnaire (BRIEF)
This questionnaire is filled out by parents of children and adolescents between the ages of 6 and 18 years. Different areas of executive functioning are addressed in 75 questions that form 8 subscales: Inhibition, Cognitive Flexibility/Shifting, Emotional Control, Initiate, Working-memory, Plan/organize, Organization of materials, Monitor. The 8 subscales make up two indices: Behavior Regulation Index (ability to adjust thinking and regulate emotions and behavior) and Metacognition Index (ability to independently carry out tasks and solve problems based on the judgment of own behavior). A total executive functioning score can be derived as well (13, 14).

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